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ARIANI, KADE

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

ATTACHMENT TO ADVOSRY ACTION

In response to Applicant arguments that Asgharian never actually suggest that glycerin be used in combination with sodium bicarbonate and the relative amounts of sodium bicarbonate and methyl trypsin used in Asgharian are quite different from those recite in claim 73. Kamien teaches 15% sodium bicarbonate is the cheapest and most effective cerumenolytic (p.817 1st column 1st paragraph lines 17-18 and p.828 2nd column 2nd paragraph). Moreover, Asgharian et al. teach the use of a water-miscible organic molecule to further enhance the stability of methyl trypsin (Al-trypsin) (column 6 lines 60-61). Asgharian et al. also teach to include 10-90% stabilizers including glycerol (a polyol) (column 7 lines 16 and 30). Therefore, Asgharian et al. suggest the use of glycerin with methyl trypsin. Moreover, Asgharian et al. teach a liquid enzyme and disinfecting composition comprising methyl trypsin in amounts of 1-100 PAU/ml (or 1 - 100 AU/ml) (column 9, lines 13-14), which is within the claimed range (about 50 AU/ml to about 500AU/ml). Asgharian et al. also teach for a solid Me-trypsin composition at least 0.2% sodium bicarbonate is used (Example 4). It must be noted that a person of ordinary skill in the art at the time the invention was made would have known that a cerumenolytic composition in order to be administer to ear must be in the form of a liquid such as ear drop, therefore the amount of buffer could have been optimized or increased to provide a liquid methyl trypsin composition. Moreover, since at the time the invention was made it was well known in the art that the optimum pH of trypsin is about 8.0, thus, a person of ordinary skill in the art would have been motivated to adjust the

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pH of the sodium bicarbonate buffer composition for trypsin to about 8.0 for optimal enzyme activity.

In response to Applicant arguments that none of the cited references suggest any benefit to the use of methyl trypsin in a cerumenolytic solution in combination with sodium bicarbonate, and that there is no suggestion in Asgharian or Hunt to use benzalkonium chloride in a cerumenolytic solution. In this case, Hunt et al. teach a liquid media including an enzyme effective to remove debris deposited material, the debris are protein-based debris, mucin-based debris, lipid based debris, and carbohydrate-based debris (column 7 lines 58-65). Hunt et al. also teach using the buffering agent sodium salt of bicarbonate to maintain the pH of a liquid medium containing trypsin in the desired range (column 6 lines 61-64 and column 7 lines 5-7, and column 8 lines 39). Hunt et al. also teach using preservatives benzalkonium chloride (0.001% or more) (column 6 lines 51 and 60). Please note that benzalkonium chloride is a surfactant and a disinfectant. Moreover, it must be noted that at the time the invention was made the presence of proteins including keratin debris (up to 60%), lipids, and carbohydrates in the cerumen plugs (ear wax) was known in the art. And it was known in the art that trypsin was able to solubilize keratin. Therefore, because Kamien teaches a 15% sodium bicarbonate solution is an effective cerumenolytic, a person of ordinary skill in the art could have been motivated to modify the composition as taught by Kamien by adding methyl trypsin and benzalkonium chloride according to the teachings of Hunt et al. in the cerumenolytic solution of Kamien with a reasonable expectation of success, to

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provide a cerumenolytic composition. The motivation would be to improve cerumenolytic activity of the composition due to the presence of trypsin (keratin solubilization) and lipid solubilization by benzalkonium chloride (surfactant), and also to increase the shelf life (preservative and disinfecting activities of benzalkonium chloride). Moreover, a person of ordinary skill in the art at the time the invention was made could have been motivated to use glycerol according to the teachings of Asgharian et al. to further enhance the stability of methyl trypsin. As indicated in MPEP as long as some motivation or suggestion to combine the references is provided by the prior art taken as a whole, the law does not require that the references be combined for the reasons contemplated by the inventor. See *In re Beattie*, 974 F.2d 1309, 24 USPQ2d 1040 (Fed. Cir. 1992); *In re Kronig*, 539 F.2d 1300, 190 USPQ 425 (CCPA 1976) and *In re Wilder*, 429 F.2d 447, 166 USPQ 545 (CCPA 1970).

Applicant arguments regarding unexpected results, and the discovery of synergistic effect by combination of the ingredients of claim 73, is not persuasive, because, synergism is when the effect is greater than the sum of the individual effects. In this case, according to the specification (p. 34 Table 8, 2nd 3rd and 4th columns line 1 and p.23 Table 1 which disclose the ingredients), the absorbance at 280 nm (human), which indicates the amount of protein digested by the composition, for composition D (5% sodium bicarbonate, 200 AU/ml methyl trypsin, 7% glycerin, 0.01 % benzalkonium chloride) is 1153, for D1 composition (5% sodium bicarbonate, 7% glycerin, 0.01 % benzalkonium chloride) is 897, for D2 composition (200AU/ml methyl trypsin, 7%

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glycerin, 0.01 % benzalkonium chloride) is 716, and for 5% sodium bicarbonate solution is 1169. Accordingly, the sum of the absorbance(s) for D1+D2 is $897+716$ which is equal to 1613, which is higher than 1153 (composition D, combination of methyl trypsin and sodium bicarbonate). As mentioned immediately above, synergism is when the total effect is greater than the sum of the individual effects. In this case the total absorbance (effect) is 1153, which is less than the sum of the individual absorbance (effects) 1613.

/Leon B Lankford/
Primary Examiner, Art Unit 1651